

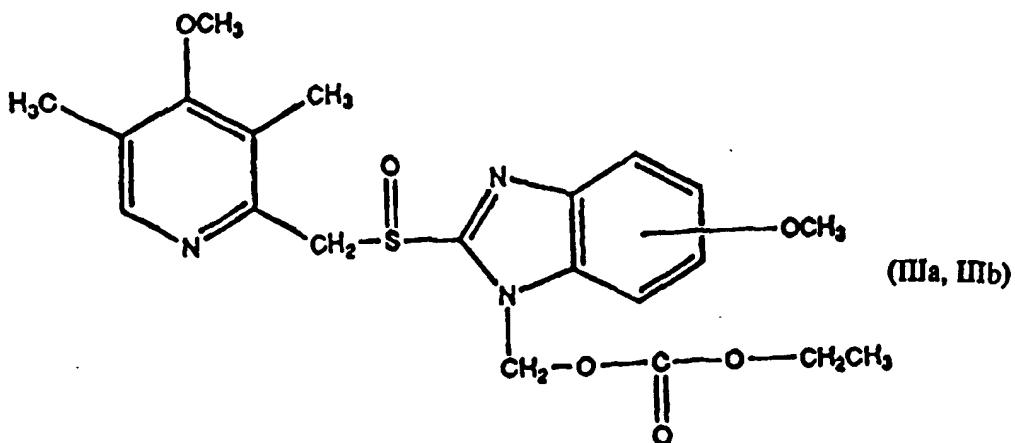


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A1	(11) International Publication Number: WO 95/32957
C07D 401/12, A61K 31/44		(43) International Publication Date: 7 December 1995 (07.12.95)

(21) International Application Number: PCT/SE94/00512	(81) Designated States: US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
(22) International Filing Date: 27 May 1994 (27.05.94)	
(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).	Published <i>With international search report.</i>
(72) Inventor; and	
(75) Inventor/Applicant (for US only): VON UNGE, Sverker [SE/SE]; Alvägen 4, S-430 33 Fjärås (SE).	
(74) Agent: LARSSON, Birgitta; Astra Aktiebolag, Patent Dept., S-151 85 Södertälje (SE).	

(54) Title: NOVEL ETHOXYSARBOXYLOXYMETHYL DERIVATIVES OF SUBSTITUTED BENZIMIDAZOLES



IIIa (+)-enantiomer

IIIb (-)-enantiomer

(57) Abstract

The novel optically pure compounds, i.e. the single enantiomeric compounds, (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, (-)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

NOVEL ETHOXCARBONYLOXYMETHYL DERIVATIVES OF SUBSTITUTED BENZIMIDAZOLES

Field of the invention

5

The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation.

10 Background of the invention

The compound 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, having the generic name omeprazole is described in EP 5129. Omeprazole is an effective gastric acid secretion inhibitor, and is useful as an 15 antiulcer agent.

A number of alkoxy carbonyloxy methyl derivatives of omeprazole are disclosed in EP 0233284. The compounds, omeprazole as well as its N-substituted derivatives, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical 20 isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as lower degree of interindividual variation. The present invention provides such compounds, which are novel single enantiomers of ethoxy-carbonyloxy methyl derivatives of omeprazole.

25

The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution.

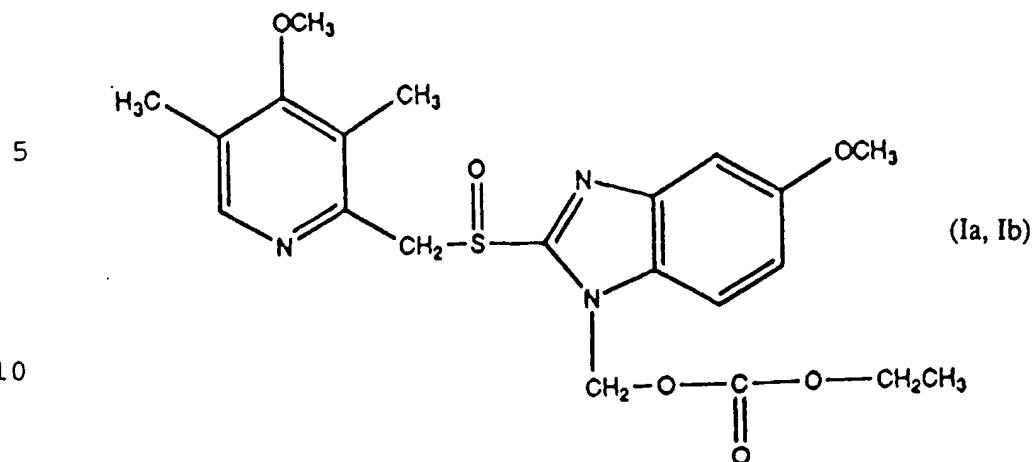
30

There is no example given in the prior art of the isolated and characterized compounds of the invention.

Detailed description of the invention

35

The present invention refers to the new single enantiomers of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate according to compounds Ia and Ib



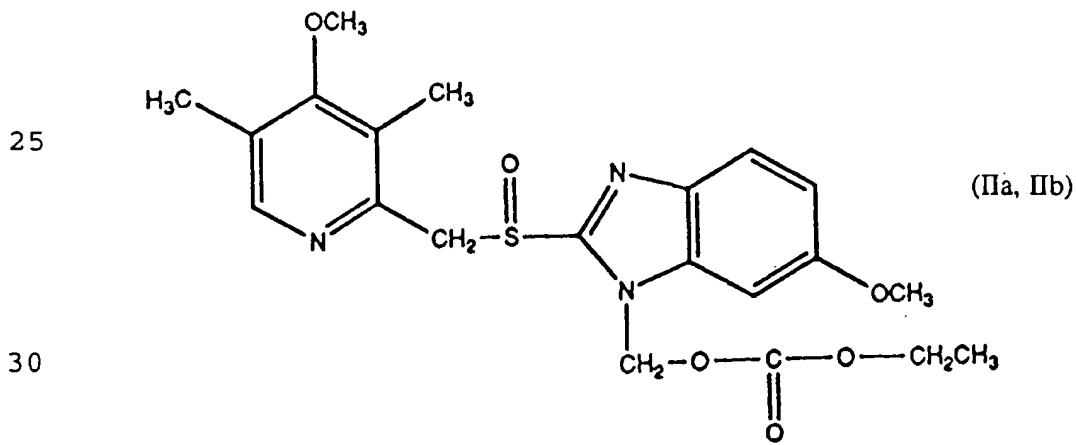
Ia (+)-enantiomer

Ib (-)-enantiomer

15

20

as well as the new single enantiomers of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate according to compounds IIa and IIb.



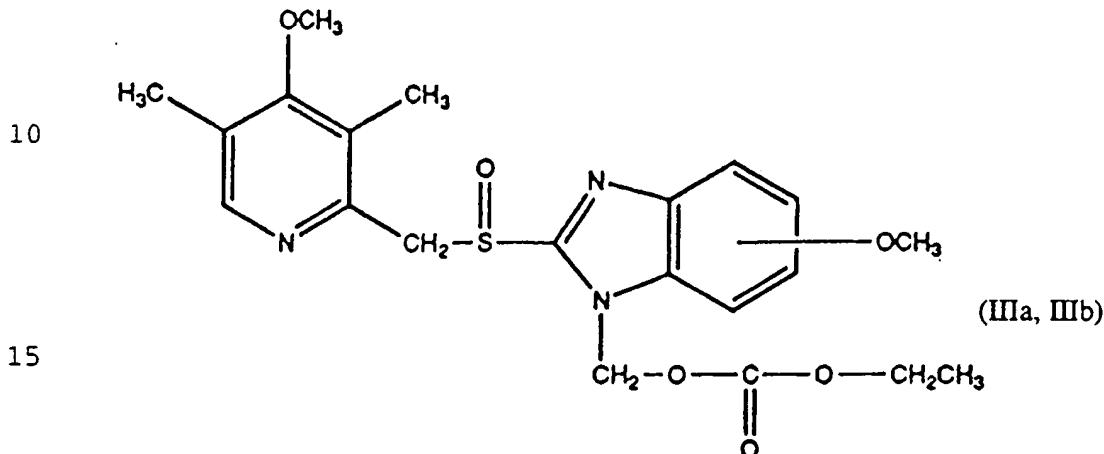
IIa (+)-enantiomer

IIb (-)-enantiomer

35

The invention also refers to the new single enantiomers of the regiosomeric mixture

of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-ylmethyl ethyl carbonate and 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-ylmethyl ethyl carbonate according to compounds IIIa and IIIb, wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6.



IIIa (+)-enantiomer

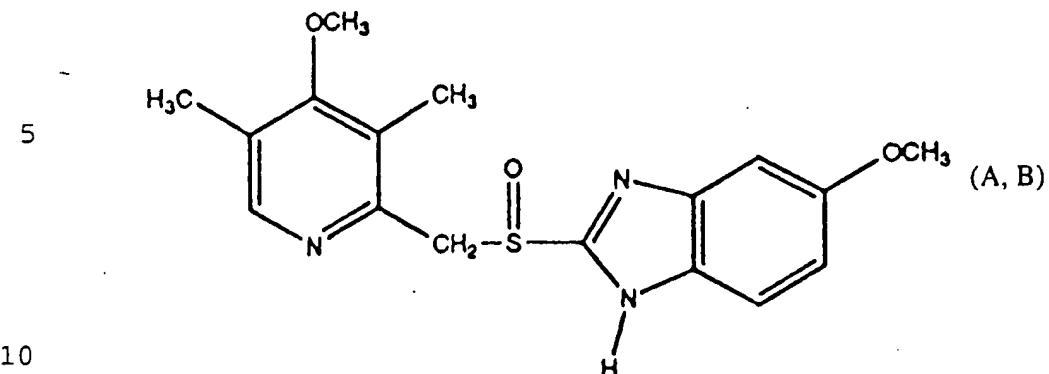
IIIb (-)-enantiomer

20

With the expression "optically pure compound of the invention" is meant the (+)-enantiomer of said compound (or compounds) essentially free of the corresponding (-)-enantiomer and the (-)-enantiomer essentially free of the corresponding (+)-enantiomer, respectively.

25

It is believed that the compounds of invention is metabolized into the corresponding compounds, carrying H in the N-1 position in the benzimidazole nucleus (compounds A and B, i.e. the single enantiomers of omeprazole) before exerting its effect.



A (+)-omeprazole

B (-)-omeprazole

15

Single enantiomers of omeprazole in neutral form (i.e. not as salts thereof) have hitherto only been obtained as syrups and not as crystalline products. However, the optically pure N-ethoxycarbonyloxymethyl derivatives, both the single enantiomers of pure regioisomers (i.e. the 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate isomer and the 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate isomer) as well as the single enantiomers of regioisomeric mixtures are obtained as crystalline products.

25 Therefore, it is possible to obtain crystalline products, which would be easier to handle (use) in the preparation of pharmaceutical formulations than a syrup of the single enantiomers of omeprazole in neutral form.

30 Further, it is possible to use the single enantiomers of ethoxycarbonyloxymethyl derivatives of omeprazole to obtain the single enantiomers of omeprazole in neutral form in a higher purity.

35 The optically pure compounds do not undergo directly racemization in neutral pH, which was surprising since N-substituted omeprazole derivatives, catalyzed by protons, are converted to achiral sulfenic acids which easily undergo the reverse reaction back to sulfoxides (see e.g. Brändström *et al.* Acta Chemica Scandinavica 43 (1989) 587). It is obvious that such a reversible reaction from an achiral sulfenic acid back to a sulfoxide would cause a racemic compound. This high stability towards

racemization in neutral pH combined with the assumption that the compounds will be dissolved and converted to optically pure omeprazole in the intestine but not in the acidic compartments of the stomach makes it possible to use a single enantiomeric compound of invention in therapy.

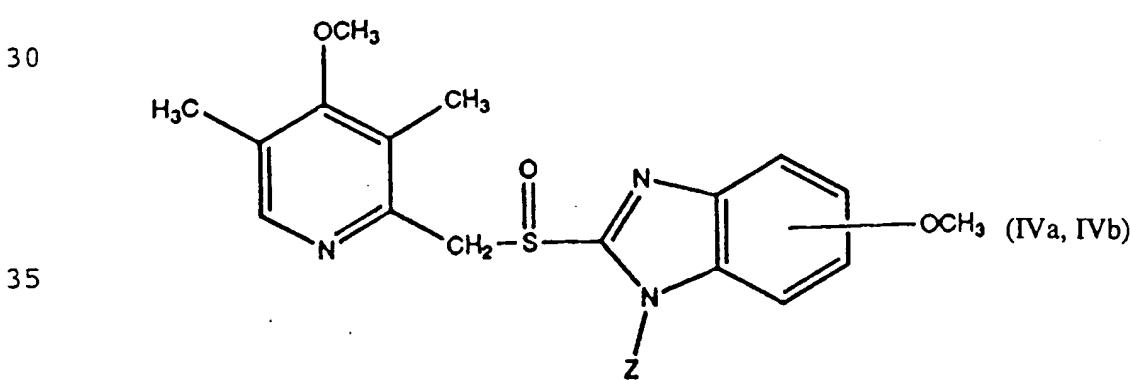
5

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the single enantiomeric compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as 10 gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They 15 may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compounds of the invention may also be useful in the treatment of psoriasis as well as in the treatment 20 of Helicobacter infections.

Preparation

The optically pure compounds of the invention, i.e. the single enantiomers may be 25 prepared according to one of the following methods a), b) or c) described below.

a) Reacting a compound of the formula IVa) or IVb).



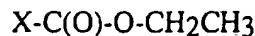
IVa (+)-enantiomers

IVb (-)-enantiomers

5

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6 and wherein Z is either a metal cation such as Na^+ , K^+ , Li^+ or Ag^+ or a quaternary ammonium ion, such as tetrabutylammonium, with chloromethyl ethyl carbonate.

10 b) Reacting a compound of the formula IVa) or IVb) either in the form of a pure regioisomer or as a regiosomeric mixture, wherein Z is hydroxymethyl, with a compound of the formula V,

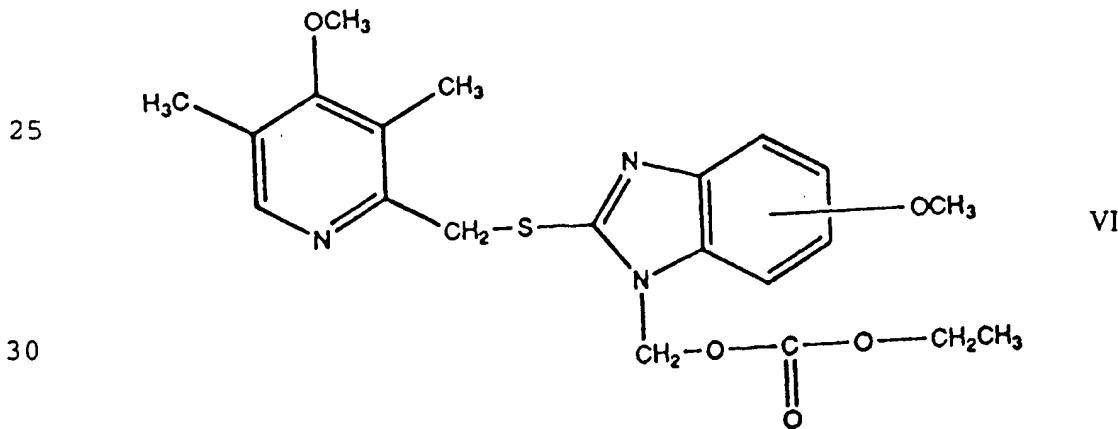


V

15

wherein X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in the presence of a suitable base such as triethylamine.

20 c) Oxidizing a compound of the formula VI either as a pure regioisomer or as a regiosomeric mixture, wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6.



35 This oxidation may be carried out by using a chiral inducing oxidizing agent or by using an oxidizing agent with a chiral catalyst or any other chiral environment such as e.g. chiral solvents.

The oxidation may also be carried out enzymatically by using an oxidizing enzyme or

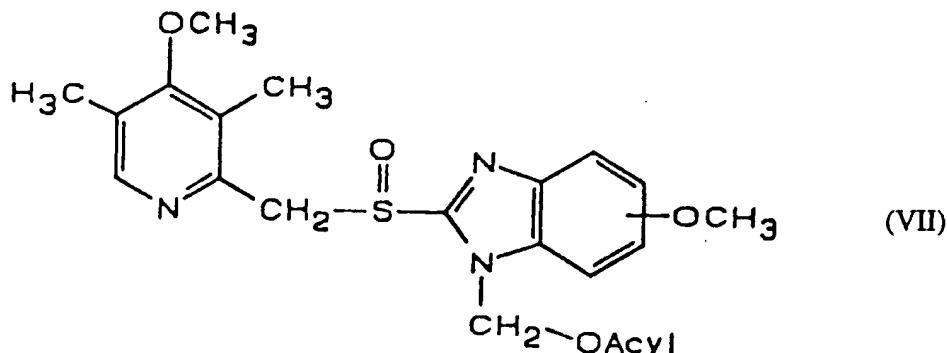
microbiologically by using a suitable microorganism.

The reactions according to methods a) and b) above are suitably carried out under protective gas in the absence of water. Suitable solvents are acetonitrile, 1-methyl-2-pyrrolidinone, acetone or dimethyl formamide or hydrocarbons such as toluene or benzene or halogenated hydrocarbons such as methylene chloride or chloroform. The reactions may be carried out at a temperature between the ambient temperature and the boiling temperature of the reaction mixture.

10 The starting compounds IVa) and IVb), respectively, being salt of the single enantiomers of omeprazole, can be prepared by separating the two stereoisomers of a diastereomeric mixture of the following type 5- or 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula VII

15

20



25

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

30 The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

35 The diastereomeric esters can be separated either by chromatography or fractional

crystallization.

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolysed off by a base in an 5 aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

To obtain the sodium salt of single enantiomers of omeprazole, the resulting 10 compound is treated with a base, such as NaOH , in an aqueous or nonaqueous medium, or with NaOR^2 where R^2 is an alkyl group containing 1-4 carbon atoms, or with NaNH_2 . In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

15 When mixtures of regioisomers are obtained in any of the above methods, a pure regioisomer of a single enantiomer of the invention can be isolated by means of crystallization or chromatography.

In those cases when a mixture of the two enantiomers are obtained, the single 20 enantiomers can be separated according to known methods, e.g. by crystallisation from different solvents.

In some cases the starting materials utilized in the methods a)-c) are unknown. These 25 unknown starting materials may be obtained from known compounds by utilizing processes known per se.

Chloromethyl ethyl carbonate may be obtained from ethanol by treatment with chloromethyl chloroformate in the presence of pyridine.

30 Intermediates of formula IV, wherein Z is hydroxymethyl are obtained by reaction of the corresponding single enantiomer of omeprazole with formaldehyde.

Starting materials of the formula V may be obtained by known methods, e.g. from 35 ethanol by treatment with phosgene or 1,1'-carbonyl diimidazole or p-nitrophenyl chloroformate.

Starting materials of formula IV and VI can be obtained from the regioisomeric mixtures of the corresponding compounds by means of crystallization or

chromatography.

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories

which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or 5 they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of 10 the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid 15 preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

The typical daily dose of the active compound will depend on various factors such as 20 for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.

Example 1. Preparation of (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

(+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole sodium salt 3.0 g (8.2 mmol) was dissolved in water (200 ml). The 30 solution was neutralized with an aqueous solution of ammonium chloride and thereafter extracted with methylene chloride. The organic phase was dried over Na₂SO₄, filtered and then removed by film evaporation. The oily residue containing (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole was dissolved in acetonitrile (50 ml). Potassium carbonate (1.2 g, 9.0 35 mmol) together with chloromethyl ethyl carbonate (1.2 g, 9.0 mmol) was added and the mixture was stirred over night. After evaporation the residue was partitioned between water and methylene chloride. The aqueous phase was pH adjusted to pH 9

with aqueous ammonia. The layers were separated and the organic phase was dried over Na_2SO_4 . After filtration the solvent was evaporated off. The product which consisted of approximately equal amounts of the two regioisomers was crystallized when a small amount of acetonitrile was added. There was obtained 3.3 g (90%) of 5 the title compounds as white crystals m.p. 81-96°C. $[\alpha]^{20}_D = -121.4$ (c=1%, chloroform).

NMR data are given below

10 Example 2. Preparation of (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

15 (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole sodium salt 3.0 g (8.2 mmol) was dissolved in 1-methyl-2-pyrrolidinone (50 ml). Chloromethyl ethyl carbonate (1.2 g, 9.0 mmol) was added and the mixture was stirred over night. The reaction mixture was partitioned between water and methylene chloride. The organic layer was washed repeatedly with water 20 and then dried over Na_2SO_4 . After evaporation the product was purified by flash chromatography on silica gel with a mixture of acetonitrile/methylene chloride as eluent. The solvents were removed by film evaporation and there was obtained 2.4 g (66%) of the title compounds as white crystals m.p. 83-100°C. $[\alpha]^{20}_D = +122.8$ (c=1%, chloroform).

25 NMR data are given below

Example 3. Preparation of (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

30 Starting from 2.9 g of the regioisomeric mixture of (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate from 35 Example 1 the regioisomers of the (-)-enantiomer was separated by repeated recrystallisations from 2-propanol in which the title compound was somewhat less soluble. 76 mg of the title compound containing less than 8% of the other regioisomer was isolated. The product was obtained as white crystals,

m.p. 115-119°C.

NMR data are given below.

5 Example 4. Preparation of (-)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate

Starting from 2.9 g of the regioisomeric mixture of (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate from Example 1 the regioisomers of the (-)-enantiomer was separated by repeated recrystallisations from 2-propanol in which the title compound was somewhat more soluble. 30 mg of the title compound containing less than 8% of the opposite regioisomer was isolated. The product was obtained as white crystals, m.p. 97-100°C.

NMR data are given below.

Table 1.

20

Ex.	Solvent	NMR data δ ppm
-----	---------	----------------

25

1.	CDCl ₃ 300 MHz	1.3 (m, 3H), 2.2-2.3 (m, 6H), 3.71 (s, 3H), 3.86 and 3.90 (two singlets, 3H), 4.18-4.27 (m, 2H), 4.88 (d, 1H), 4.98 (d, 1H), 6.37-6.42 (m, 1H), 6.51-6.58 (m, 1H), 6.96-7.26 (m, 2H), 7.53 and 7.67 (two doublets, 1H), 8.16 (s, 1H).
----	------------------------------	---

30

2.	CDCl ₃ 300 MHz	1.3 (m, 3H), 2.2-2.3 (m, 6H), 3.70 (s, 3H), 3.84 and 3.89 (two singlets, 3H), 4.17-4.26 (m, 2H), 4.87 (d, 1H), 4.97 (d, 1H), 6.36-6.42 (m, 1H), 6.50-6.57 (m, 1H), 6.95-7.26 (m, 2H), 7.53 and 7.67 (two doublets, 1H), 8.15 (s, 1H).
----	------------------------------	---

35

3.	CDCl ₃ 300 MHz	1.28 (s, 3H), 2.20 (s, 3H), 2.24 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.21 (q, 2H), 4.87 (d, 1H), 4.97 (d, 1H), 6.38 (d, 1H), 6.52 (d, 1H), 7.05 (dd, 1H), 7.24 (d, 1H), 7.53 (d, 1H), 8.15 (s, 1H).
----	------------------------------	--

13

4. CDCl_3 1.30 (s, 3H), 2.22 (s, 3H), 2.24 (s, 3H), 3.70 (s, 3H),
500 MHz 3.90 (s, 3H), 4.23 (q, 2H), 4.88 (d, 1H), 4.97 (d, 1H),
6.41 (d, 1H), 6.55 (d, 1H), 6.98 (dd, 1H), 7.10 (d, 1H),
7.67 (d, 1H), 8.16 (s, 1H).

5

Preparation of the starting compounds used in Examples 1 and 2 are described in the following examples. Further some intermediates used in said preparation of the starting compounds are described by examples.

10

Example 5. Preparation of (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-
15 methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed
20 precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity (*e.e.*) which was analyzed by chiral column chromatography was $\geq 99.8\%$.
[α]²⁰_D = +42.8° (c=0.5%, water).

25 NMR data are given below.

Example 6. Preparation of (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

30 100 mg (0.3 mmol) of (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-
methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (-)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 μl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed
35 precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247-249°C. The optical purity (*e.e.*) which was analyzed by chiral column chromatography was $\geq 99.8\%$.

$[\alpha]^{20}_D = -44.1^\circ$ (c=0.5%, water).

NMR data are given below.

5 Table 2

	<u>Ex.</u>	<u>Solvent</u>	<u>NMR data</u>	<u>ppm</u>
10	5.	DMSO-d ₆ 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).	
15	6.	DMSO-d ₆ 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).	

Example 7. Preparation of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-
(R/S)-sulfinyl]-1-[
(R)-mandeloyloxymethyl]-1H-benzimidazole

20 A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over MgSO₄ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

30 NMR data are given below.

Example 8. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-
(R/S)-sulfinyl]-1-[
(R)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 7 were separated using reversed

phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na_2SO_4 and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.

15 NMR data are given below.

Example 9. Preparation of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]- (R/S) -sulfinyl]-1-[(S) -mandeloyloxymethyl]-1H-benzimidazole

20 The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 7. Recrystallization from 100 ml acetonitrile yielded 25 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below.

Example 10. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]- (R/S) -sulfinyl]-1-[(S) -mandeloyloxymethyl]-1H-benzimidazole

30 The diastereomers of the title compound in Example 9 were separated using reversed phase chromatography (HPLC) in the same way as in Example 8, but using the diastereomeric mixture of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]- (R/S) -sulfinyl]-1-[(S) -mandeloyloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 8. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colourless syrup.

NMR data are given below.

Example 11. Preparation of (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-

5 pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) 10 sodium hydroxid in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 μ l (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic 15 solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]^{20}_D = -155^\circ$ (c=0.5%, chloroform).

20 NMR data are given below

Example 12. Preparation of (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-

pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

25 0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) 30 sodium hydroxid in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and 25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 μ l (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x25 ml dichloromethane. The organic 35 solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]^{20}_D = +157^\circ$ (c=0.5%, chloroform).

NMR data are given below

Table 3.

	<u>Ex.</u>	<u>Solvent</u>	<u>NMR data ppm</u>
5	7.	CDCl ₃ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
10	8.	CDCl ₃ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
15	9.	CDCl ₃ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
20	10.	CDCl ₃ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
25	11.	CDCl ₃ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.19 (s, 1H).
30	12.	CDCl ₃	2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m, 2H), 6.94 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.20 (s, 1H).
35			

The best mode of carrying out the invention known at present is to use the compounds described in Example 3 and Example 4.

Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

5 Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

10	Compounds according to Example 1	1.0 g
	Sugar, powder	30.0 g
	Saccharine	0.6 g
	Glycerol	5.0 g
	Flavouring agent	0.05 g
15	Ethanol 96%	5.0 g
	Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compounds was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Tablets

25 A tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compounds according to Example 2	500 g
30	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
35	Distilled water	q.s.
II	Hydroxypropyl methylcellulose	3 g
	Polyethylene glycol	19 g

Colour Titanium dioxide	4 g
Purified water	313 g

I Compounds according to Example 2 was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10.000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

10

II A solution of hydroxypropyl methylcellulose and polyethylene glycol in purified water was prepared. After dispersion of titanium dioxide the solution was sprayed onto the tablets I in an Accela CotaR, Manesty coating equipment. A final tablet weight of 125 mg was obtained.

15

Capsules

20

Capsules containing 30 mg of active compound were prepared from the following ingredients:

25

Compounds according to Example 2	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

30

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

35

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 600 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

Coating solution:

20

	Hydroxypropyl methylcellulose phthalate	70 g
	Cetyl alcohol	4 g
	Acetone	600 g
5	Ethanol	200 g

The final coated pellets were filled into capsules.

Suppositories

10

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

15

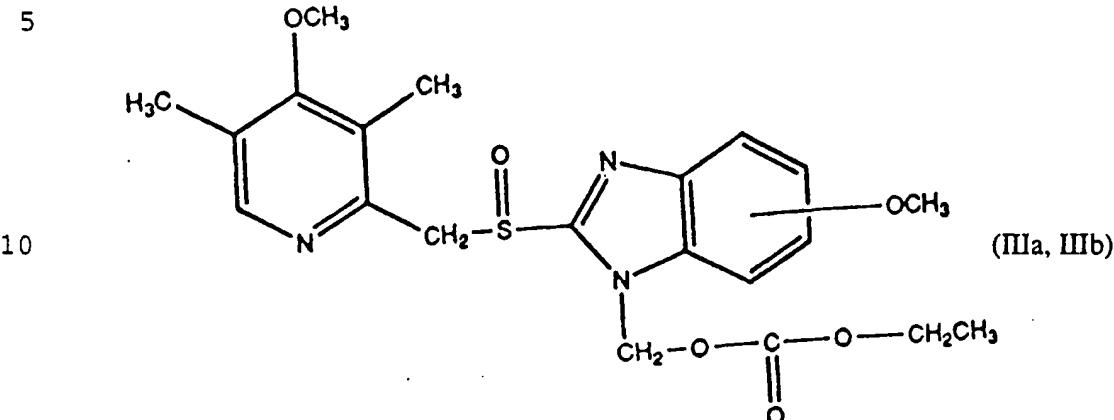
Compounds according to Example 1	4 g
Witepsol H-15	180 g

20

The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Claims

1. Single enantiomeric compounds having the formula IIIa and IIIb



IIIa (+)-enantiomer
IIIb (-)-enantiomer

20 wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6.

2. Compounds according to claim 1, characterized in that the compounds are (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, (-)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate, (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

30 3. Compounds according to claim 1 characterized in that the compounds are (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (-)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

35 4. Compounds according to claim 1 characterized in that the compounds are (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate and (+)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole-1-ylmethyl ethyl carbonate.

5. Compound according to claim 1 characterized in that the compound is (-)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-ylmethyl ethyl carbonate substantially free of its (+)-enantiomer.

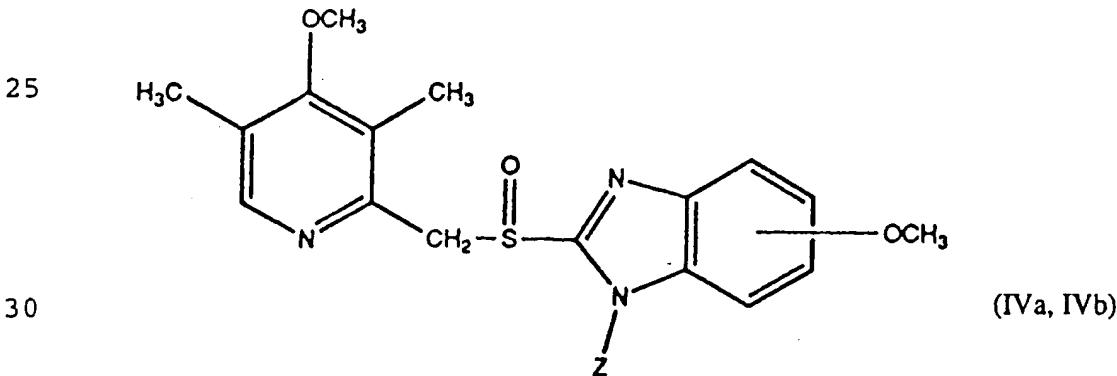
10. 6. Compound according to claim 1 characterized in that the compound is (-)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-ylmethyl ethyl carbonate substantially free of its (+)-enantiomer.

15. 7. Compound according to claim 1 characterized in that the compound is (+)-5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-ylmethyl ethyl carbonate substantially free of its (-)-enantiomer.

20. 8. Compound according to claim 1 characterized in that the compound is (+)-6-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-ylmethyl ethyl carbonate substantially free of its (-)-enantiomer.

9. A process for the preparation of compounds according to claim 1 characterized by

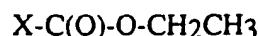
25. a) reacting a compound of the formula IVa) or IVb)



35. IVa, (+)-enantiomers
IVb, (-)-enantiomers

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein Z is either a metal cation such as Na^+ , K^+ , Li^+ or Ag^+ or a quaternary ammonium ion, such as tetrabutylammonium, with chloromethyl ethyl carbonate,

5 b) reacting a compound of the formula IVa) or IVb) either in the form of a pure regioisomer or as a regioisomeric mixture, wherein Z is hydroxymethyl, with a compound of the formula V,



V

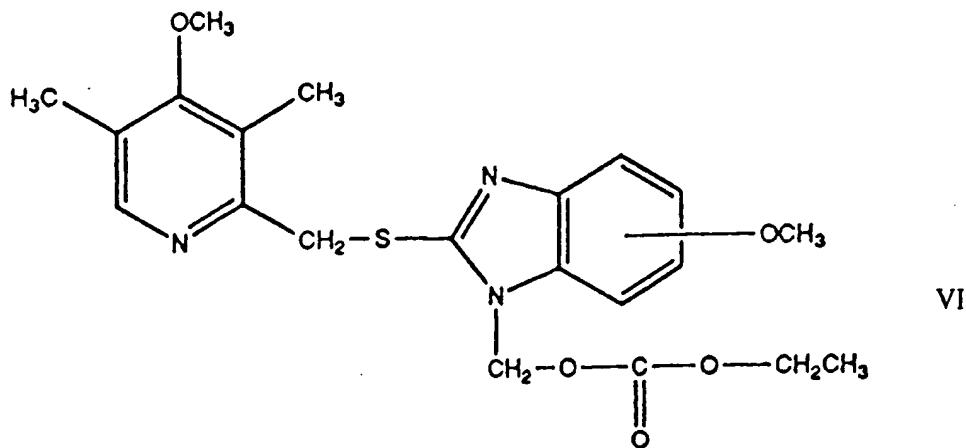
10

wherein X is Cl or imidazole or p-nitrophenoxy or a functionally equivalent group, in the presence of a suitable base such as triethylamine, or

15

c) oxidizing a compound of the formula VI either as a pure regioisomer or as a regioisomeric mixture,

20



25

30 and when mixtures of regioisomers are obtained in any of the above methods the pure regioisomeric compound is isolated by crystallisation or chromatography.

35

10. Pharmaceutical preparation comprising a single enantiomeric compound according to any of claims 1-8 as active ingredient.

11. Single enantiomeric compounds according to any of claims 1-8 for use in therapy.

12. Use of a single enantiomeric compound according to any of claims 1-8 in the manufacture of a pharmaceutical formulation for inhibiting gastric acid secretion.
13. Use of a single enantiomeric compound according to any of claims 1-8 for the manufacture of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.
14. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.
15. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an enantiomeric compound according to any of claims 1-8.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00512

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 401/12, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5021433 (T.B. ALMINGER ET AL), 4 June 1991 (04.06.91) -----	1-13

 Further documents are listed in the continuation of Box C. See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

18 November 1994

Date of mailing of the international search report

13-01-1995

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86Authorized officer
Göran Karlsson
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 94/00512

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 14-15
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy,
see Rule 39.1
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/94

International application No.

PCT/SE 94/00512

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5021433	04/06/91	AU-B- 598491	28/06/90
		AU-A- 6542986	19/05/87
		CN-B- 1022487	20/10/93
		DE-A- 3686483	24/09/92
		EP-A- 0221041	06/05/87
		EP-A,B- 0233284	26/08/87
		SE-T3- 0233284	
		ES-T- 2051696	01/07/94
		FI-C- 91151	25/05/94
		JP-T- 63501151	28/04/88
		WO-A- 8702668	07/05/87